THE U.S. DEPARTMENT OF DEFENSE PHARMACOECONOMIC CENTER

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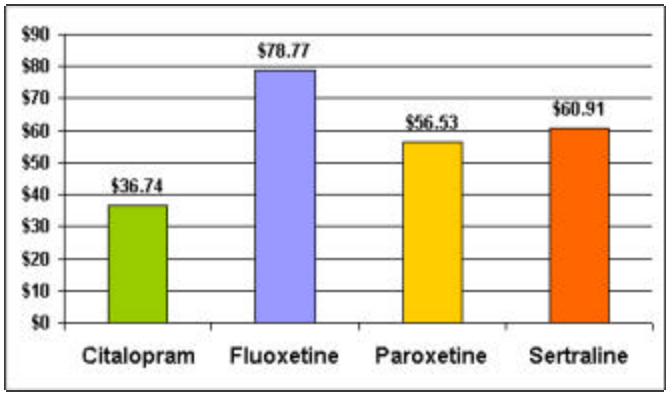
Cost-Effective Use of SSRIs

Increasing Citalopram Usage Can Reduce Drug Costs in Military Treatment Facilities

Summary

- All Selective Serotonin Reuptake Inhibitors (SSRIs) appear to be equally efficacious for the treatment of depression.
- The SSRIs cause adverse effects at similar rates, although the incidences of individual adverse effects (e.g., sedation) differ. There are no statistically significant differences in study completion rates, discontinuation rates, or dropouts due to adverse events. DoD/VA Clinical Practice Guidelines for Depression find "insufficient evidence to prefer any one SSRI for all patients on the basis of efficacy or side effect profile."
- The SSRIs are metabolized by different cytochrome P450 pathways and differ in their propensity to cause drug interactions. Citalopram and sertraline are less likely to cause cytochrome P450 drug interactions than paroxetine and fluoxetine.
- The SSRIs have the 3rd highest drug class expenditure in DoD—a total of $60 million at Military Treatment Facilities (MTFs) in FY00.
- Citalopram has the lowest cost per 30-day supply and the lowest weighted average cost per prescription compared to other SSRIs. Generic competition (generic version of Prozac®) in this drug class is not expected until August 2001 at the earliest.
- Citalopram is the most cost-effective agent in this drug class. MTFs can reduce drug costs by using citalopram for patients newly diagnosed with depression unless there is a clinical reason to use another SSRI.

Weighted Average Cost per SSRI Prescription in MTFs*



* Based on SSRI dose distributions and quantities dispensed in MTFs from Sep 00 to Nov 00 and DAPA prices as of Jan 2001.

All SSRIs appear to be equally efficacious for the treatment of depression.

A recent comprehensive evidence report on newer pharmacotherapies for the treatment of depression concluded that there are no significant efficacy differences among newer antidepressants for treating adults with major depressive disorder. The review included ten head-to-head studies with SSRIs; eight of these involved a comparison of another SSRI with fluoxetine.

[The report, "Evidence Report #7, Treatment of Depression: Newer Pharmacotherapies," was commissioned by the Agency for Healthcare Research and Quality (formerly the Agency for Health Care Policy and Research) and is available online from the National Library of Medicine's Health Service/Technology Assessment Text service at **http://text.nlm.nih.gov**.]

Citalopram was approved by the FDA for U.S. marketing in 1998 after being marketed in Europe since 1989.[3] Forest Pharmaceuticals, the manufacturer of citalopram (Celexa®), reports worldwide experience in over 20 million patients, and a large body of clinical literature supporting the safety and efficacy of citalopram is available. Several recent review articles address the use of citalopram for depression.[1-4]

Based on the results of four head-to-head trials comparing citalopram to fluoxetine, sertraline, or fluvoxamine (not marketed for depression in the US), citalopram appears to be equally effective to the other SSRIs in treating clinically depressed patients. There are no head-to-head trials comparing citalopram with paroxetine. A brief summary of the comparative trials appears in Table 1 on the next page.

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Table 1: Comparative antidepressant trials with citalopram

Trial	Study Design (duration)	Number of patients	Treatment (mg/day)	Efficacy Results (assessment method)
Patris[5]	MC, DB, R 8 weeks	357	citalopram 20 mg/d fluoxetine 20 mg/d	citalopram = fluoxetine (MADRS)
Bougerol[6]	MC, DB, R 8 weeks	316	citalopram 40 mg/d fluoxetine 20 mg/d	citalopram = fluoxetine (MADRS, HamD, CGI)
Eskselius[7]	MC, DB 24 weeks	400	citalopram 20-60 mg/d* sertraline 50-150 mg/d*	citalopram = sertraline (MADRS, CGI)
Haffmans[8]	MC 6 weeks	217	citalopram 30-40 mg/d*** fluvoxamine 150-200 mg/d***	citalopram = fluvoxamine** (HamD, CGI)

MC = multi-center; **DB** = double-blind; **R** = randomized
MADRS = Montgomery-Asberg Depressions Rating Scale
HamD = Hamilton Depression Scale
CGI = Clinical Global Improvements Scale

* Dosage increases allowed after week 4. Mean dosages week 24: sertraline, 82.4 mg; citalopram 33.9 mg
** Fluvoxamine is not marketed for the treatment of depression in the U.S.
*** Started at 20 mg citalopram or 100 mg fluvoxamine for one week, then increased to 30 mg citalopram or 150 mg (2 divided doses) fluvoxamine for three weeks. Increases to 40 mg citalopram or 200 mg fluvoxamine allowed at week 4. Percentage of patients receiving higher dosages: 63.8% in citalopram group, 59.6% in fluvoxamine group.

SSRIs cause adverse effects at similar rates, although the incidences of individual adverse effects differ. There are no statistically significant differences in study completion rates, discontinuation rates, or dropouts due to adverse events.

The SSRIs are commonly accepted to have a more generally favorable adverse effect profile than tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs). Major adverse effects of SSRIs include headache, diarrhea, insomnia, nausea, and sexual side effects. SSRI side effects are most prominent during therapy initiation, and then decrease in both frequency and severity within the first several weeks of treatment. Initiating therapy at low doses can minimize tolerability problems. The incidence of particular side effects differs with specific SSRIs, but overall tolerability of the SSRIs, including citalopram, appears to be similar. Price et al (1996) characterize the SSRIs as well tolerated and presenting similar post-marketing safety profiles.[9] Citalopram's adverse effect profile appears most comparable to that of sertraline.

Published meta-analyses report minimal difference in tolerability among the SSRIs. The evidence shows no statistically significant differences in study completion rates, discontinuation rates, or dropouts due to adverse events among SSRIs. Although citalopram was not on the U.S. market at the time these studies were completed, the rate at which patients discontinued citalopram during clinical trials (16%) was similar to fluoxetine (15%), sertraline (15%), and paroxetine (20%).[9-13]

In one meta analysis of double-blind trials involving a total of 746 patients with clinical depression, the most common adverse effects of citalopram were nausea and vomiting (20%), increased sweating (18%), dry mouth (17%) and headache (17%).[10] Other effects that occur at a significantly higher rate with citalopram than with placebo are ejaculation failure, diarrhea, tremor, and somnolence. As with all the SSRIs, sexual dysfunction (including decreased libido, anorgasmia, ejaculation dysfunction, and impotence) can occur in men and women taking citalopram. A recent review article summarized SSRI adverse effects (see Table 2).

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The DoD/VA Clinical Practice Guideline for Depression finds "insufficient evidence to prefer any one SSRI for all patients on the basis of efficacy or side effect profile."

The DoD/VA Clinical Practice Guideline for the Management of Major Depressive Disorder in Adults notes that although differences in drug characteristics may influence the selection of a specific SSRI for a given patient, there is "insufficient evidence to prefer any one SSRI for all patients on the basis of efficacy or side effect profile." The guideline is available at **www.cs.amedd.army.mil/Qmo** (click on "Practice Guidelines").

Citalopram and sertraline are less likely to cause cytochrome P450 drug interactions than paroxetine and fluoxetine.

The SSRIs affect the hepatic cytochrome P450 enzyme system, but vary markedly in their ability to cause inhibition of P450 subsystems.[13,14] Potential drug interactions with each of the SSRIs vary according to the P450 subsystems affected by the drug, the variability of that subsystem between individuals, and the dose given. All the SSRIs require appropriate prescribing caution and monitoring of their clinical effect.[15-22]

Randomized, controlled clinical trials or epidemiological studies have not been conducted to compare the drug interaction incidence rates between the SSRIs. Table 3 shows the variation in the degree of cytochrome P450 enzyme subsystem inhibition. Citalopram and sertraline are less potent inhibitors of CYP2D6 compared to paroxetine and fluoxetine and, in general, have the most favorable P450 drug interaction profiles.

Table 2: Percent Incidence of Adverse Effects for SSRIs* (Adapted from Reference 2)

Adverse Effect	Citalopram (N=1063) %	Fluoxetine (N=1730) %	Paroxetine (N=421) %	Sertraline (N=861) %
Anorexia	2	7	5	1
Diarrhea	3	5	4	8
Drowsiness	8	6	14	7
Dry mouth	6	4	6	7
Fatigue	2	6	10	3
Insomnia	1	7	7	8
Nausea	8	11	16	14
Nervousness	3	10	5	4
Respiratory	8	6	1	1
Sweating	2	5	9	6
Tremors	2	6	6	8

Table 3: SSRI cytochrome P450 subsystem inhibition (Adapted from Reference 3)

Enzyme	Citalopram	Fluoxetine	Paroxetine	Sertraline
CYP1A2	Unlikely	Unlikely	Unlikely	Unlikely
CYP2D6	Mild	Substantial	Substantial	Mild
CYP3A3/4	Unlikely	Mild	Unlikely	Unlikely
CYP2C9/10	No data	Contradictory information	Not clinically significant	Not clinically significant
CYP2C19	No data	Moderate	No data	Not clinically significant

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Because citalopram is 80% protein-bound (compared to protein-binding of 95-99% with other SSRIs), drug displacement interactions are not likely to occur. Like all SSRIs, concomitant therapy with MAO inhibitors is contraindicated because of the heightened risk of serotonin syndrome, characterized by mental status changes, restlessness, hyperreflexia, diaphoresis and tremor. Citalopram, sertraline, and paroxetine have half-lives of approximately 20 hours, in contrast to fluoxetine, with a half-life of 4-6 days. Among other considerations, the long half-life of fluoxetine necessitates several weeks for this drug to be completely eliminated when therapy is discontinued, important when making a change in therapy to MAOIs or TCAs.

SSRIs have the 3rd highest drug class expenditure in DoD.

DoD MTFs spent approximately $60 million on SSRIs in FY 2000, exceeded only by proton pump inhibitors ($83 million) and statins ($74 million). Clearly, any reduction in unit cost for SSRI therapy has the potential for substantially reducing MTF drug expenditures.

Citalopram has the lowest cost per 30-day supply, compared to other SSRIs.

See Table 4.

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Table 4: DAPA Prices for SSRIs as of January 2001

Drug	Strength	Cost per tablet or capsule	Cost per 30-day supply
Citalopram	20 mg 40 mg	$0.89 $0.90	**$26.70 - $27.00** (20 - 40 mg/day)
Fluoxetine	10 mg 20 mg 40 mg	$0.92* $1.29* $2.58*	**$27.60 - $77.40** (20 - 40 mg/d)
Paroxetine	10 mg 20 mg 30 mg 40 mg	$1.23 $1.14 $1.14 $1.39	**$34.20 -$41.70** (20 - 40 mg/d)
Sertraline	25 mg 50 mg 100 mg	$1.26 $1.27 $1.32	**$37.80 - $39.60** (25 - 100 mg)

* Lilly discontinued all rebate and incentive agreements for fluoxetine as of 1 Jan 2001. The prices listed here for fluoxetine are without the rebate.

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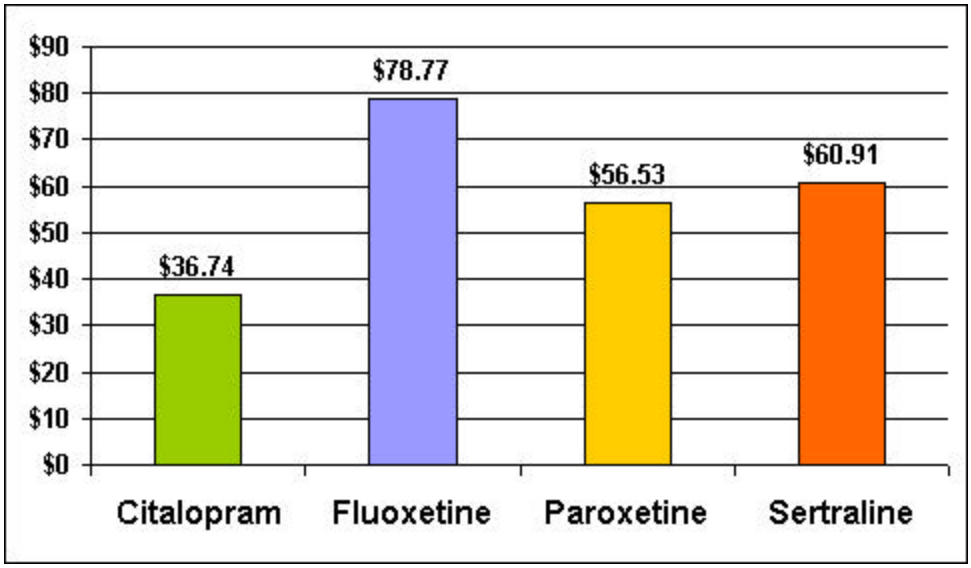
Citalopram has the lowest weighted average cost per prescription, compared to other SSRIs.

Weighted Average Cost per SSRI Prescription at MTFs*



* Based on SSRI dose distributions and quantities dispensed in MTFs from Sep 00 to Nov 00 (Source: Uniformed Services Prescription Database) and DAPA prices as of Jan 2001.

Table 5: Weighted average cost per SSRI prescription in DoD MTFs, Sep 00 through Nov 00

Drug	Strength (mg)	Rx fills by strength	Total Rx fills	Market share (% of Total Rxs)	Tab/caps per Rx	Tab/cap cost*	Cost per Rx	Weighted Average Cost Per Rx
Citalopram	20 40	10,903 12,711	23,614	10%	47 35	$0.89 $0.90	$41.57 $31.15	$36.74
Fluoxetine	10 20 40	7,647 65,577 83	73,307	30%	50 63 55	$0.92 $1.29 $2.58	$46.39 $81.71 $141.81	$78.77
Paroxetine	10 20 30 40	2,964 47,337 2,980 4,961	58,242	24%	45 50 47 40	$1.23 $1.14 $1.14 $1.39	$55.68 $56.87 $53.46 $55.24	$56.53
Sertraline	25 50 100	868 15,170 74,262	90,300	37%	44 46 47	$1.26 $1.27 $1.32	$55.47 $58.07 $61.54	$60.91

* Based on SSRI dose distributions and quantities dispensed in MTFs from Sep 00 to Nov 00 (Source: Uniformed Services Prescription Database) and DAPA prices as of Jan 2001. Cost per tab/cap for fluoxetine does not include the rebate, which was discontinued by Lilly as of 1 Jan 2001.

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Generic competition in this drug class (for Prozac®) is not expected until August 2001 at the earliest.

In August, the U.S. Court of Appeals denied the validity of the patent for fluoxetine (Prozac®; Eli Lilly) expiring in December 2003, but upheld the validity of the patent expiring Feb 2001. Generic competition for Prozac® is not expected until at least August 2001 because of the six additional months of pediatric exclusivity for Prozac® granted by the FDA. Barr Laboratories states that Barr will likely be granted approval for its abbreviated new drug application (ANDA) and start marketing a generic version of Prozac in August 2001. However, appeals processes are ongoing, and predicting the ultimate outcome of patent disputes is always risky. It is not clear whether Barr Laboratories' generic will be protected from competition from other generic manufacturers for the typical 180-day exclusivity period. Several other generic manufacturers have filed ANDAs for fluoxetine capsules.

A recent press release from Pharmaceutical Resources / Par Pharmaceuticals announced that the company had acquired marketing rights to multiple strengths of a generic version of fluoxetine (tablets, not capsules), with an expected launch date some time between August 2001 and September 2002. Historically, prices do not drop appreciably until several generic products are available.

Citalopram use is increasing at MTFs, but is still low compared to other SSRIs.

The figure below presents longitudinal market share data for the SSRIs, while Table 6 presents market share data for the SSRIs by TRICARE region.

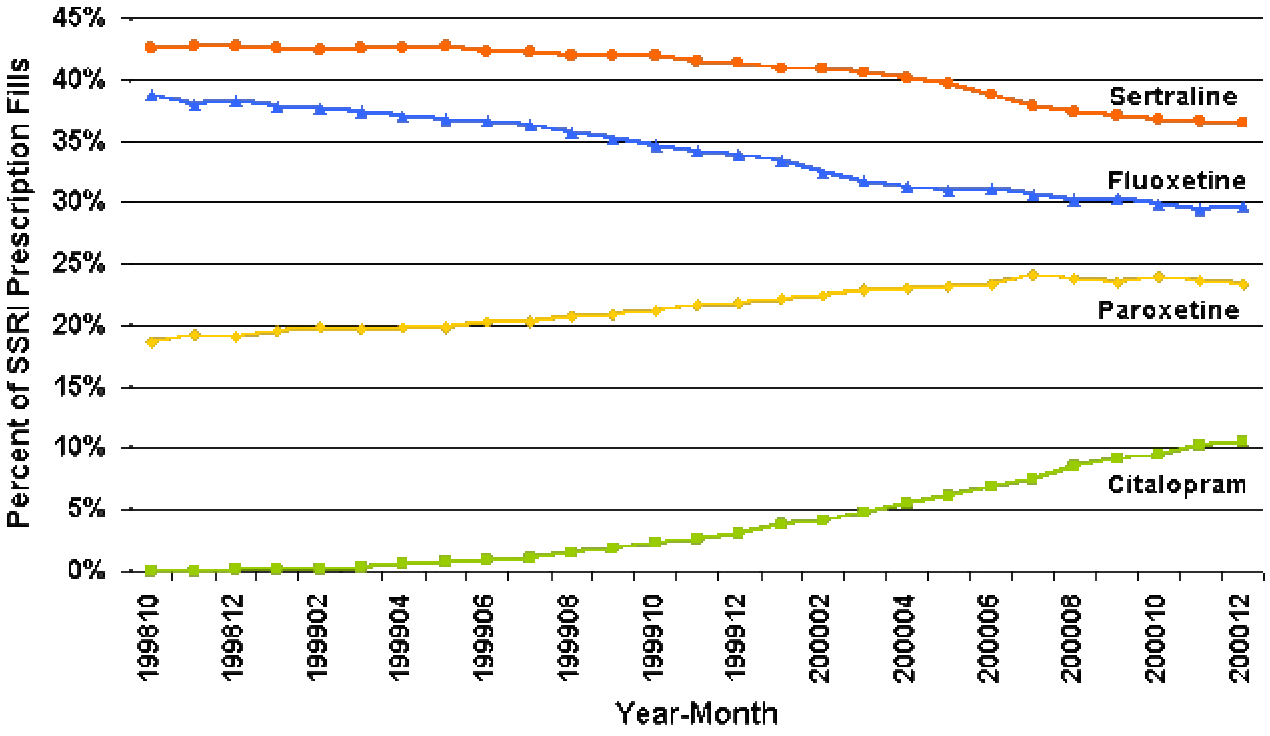

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Table 6: SSRI Prescription Distribution by TRICARE Region, Sep 00 - Nov 00

Region	Citalopram	Fluoxetine	Paroxetine	Sertraline
01	11%	31%	23%	34%
02	9%	31%	27%	33%
03	10%	30%	22%	39%
04	8%	32%	12%	48%
05	13%	26%	23%	38%
06	11%	27%	26%	36%
07	10%	29%	27%	33%
08	12%	30%	22%	36%
09	8%	27%	34%	31%
10	6%	31%	25%	39%
11	12%	25%	27%	36%
12	10%	29%	24%	37%
13	13%	36%	22%	29%
14	5%	31%	25%	39%
15	1%	33%	20%	46%
Overall	**10%**	**30%**	**24%**	**37%**

Bottom Line: Citalopram is the most cost-effective SSRI for DoD MTFs. MTFs can reduce drugs costs by by using citalopram for patients newly diagnosed with depression unless there is a clinical reason to use another SSRI.

Acknowledgement: Portions of this document were adapted from the excellent SSRI class review completed by Deborah Khachikian, PharmD, and Domenic Ciraulo, MD, Veterans Affairs Pharmacy Benefits Management and Medical Advisory Board, available from the VA Pharmacy Benefits Management Strategic Health Group's website: **www.vapbm.org**. The SSRI class review may be found at **www.vapbm.org/PBM/menu.htm** under "Drug Class Reviews."

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New Drugs and Biologics of 2000

The U.S. Food and Drug Administration (FDA) approved a total of 98 New Drug Applications (NDAs) in calendar year 2000, including 27 new molecular entities, 57 new formulations, and 8 new combination products. Complete statistics on the numbers and types of NDAs approved from 1990 to 2000 are available on the FDA website at **www.fda.gov/cder/rdmt/pstable.htm**. A list of other FDA resources for new drug and biological approvals is available in the web version of this issue of the Update at **www.pec.ha.osd.mil/Updates/0102web/Jan_01_Update_Page_3.htm.**

This article contains a list of new drugs and biologics approved in calendar year 2000, including new molecular entities, new combination products, and selected new formulations. Please see the article starting on Page 12 for a more detailed look at some of the new drugs approved at the Nov 2000 meeting of the DoD Pharmacy & Therapeutics Committee.

Cardiology

Acute Myocardial Infarction

- Tenecteplase (TNKase; Genentech); reduction of mortality associated with acute MI (approved 2 Jun 00)

Atrial Fibrillation/Atrial Flutter

- Sotalol (Betapace AF: Berlex Labs); prolongation of time to recurrence of AFib/Aflutter in symptomatic patients with or without structural heart disease, but in the absence of uncompensated CHF (approved 22 Feb 00). BetapaceAF™ is chemically identical to other sotalol HCl products (Betapace™ and its generic equivalents), but is supplied in unit-of-use packages containing specialized labeling for patients with atrial fibrillation.

Hypertension

- Candesartan / HCTZ tablets (Atacand HCT; AstraZeneca); hypertension (approved 5 Sep 00)
- Telmisartan / HCTZ tablets (Micardis HCT; Boehringer Ingelheim); hypertension (approved 17 Nov 00)

Hypercholesterolemia

- Colesevelam hydrochloride (Welchol; GelTex Pharma/Sankyo Parke Davis); reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia, administered alone or in combination with an HMG-CoA reductase inhibitor (approved 30 May 00)
- Fluvastatin extended release tablets (Lescol XL; Novartis); hypercholesterolemia (approved 6 Oct 00)

Cardiothoracic Surgery

- Bivalrudin injection – formerly known as hirulog (Angiomax; Innovex/The Medicines Co); unstable angina in patients undergoing angioplasty (approved 15 Dec 00); launch is expected Jan 01

Dermatology

- Clobetasol foam (Olux; Connetics); short-term topical treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp (approved 31 May 00)
- Diclofenac sodium gel (Solaraze; SkyePharma); actinic keratoses (approved 16 Oct 00); approved but not yet available as of Jan 2001
- Tacrolimus ointment (Protopic; Fujisawa); moderate to severe eczema in patients for whom standard therapies do not work or are not appropriate (approved 8 Dec 00)

Endocrinology

Diabetes

- Metformin / glyburide tablets (Glucovance; Bristol-Myers Squibb); type 2 diabetes (approved 31 July 00) - see Page 4 for more information
- Metformin extended release tablets (Glucophage XR, Bristol-Myers Squibb); type 2 diabetes (approved 13 Oct 00) - see Page 4 for more information
- Insulin glargine (Lantus; Aventis) once-daily administration for treatment of adults and pediatric patients with type 1 DM, or adults with type 2 DM (approved 20 Apr 00); not yet commercially available as of Jan 2001

New Drugs and Biologics of 2000

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- Insulin aspart (NovoLog; Novo Nordisk); treatment of diabetes (approved 15 Jun 00); not yet commercially available as of Jan 2001
- Nateglinide (Starlix; Novartis); monotherapy or concomitantly with metformin for type 2 DM (approved 22 Dec 00)

Testosterone Deficiency

- Testosterone Gel (Androgel; Unimed Pharmaceuticals); replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone (approved 28 Feb 00)

Osteoporosis

- Alendronate 35- and 70- mg (once weekly) tablets (Fosamax; Merck); for the prevention (35 mg) or treatment (70 mg) of osteoporosis in postmenopausal women (approved 20 Oct 00)

Gastroenterology

Bowel Cleansing

- Sodium phosphate monobasic monohydrate; sodium phosphate dibasic anhydrous (Visicol; Inkine Pharmaceutical); for cleansing of the bowel prior to colonoscopy in adults (approved 21 Sep 00) - launch expected Jan 2001

GERD

- Pantoprazole (Protonix; Wyeth Ayerst Labs); short-term treatment (up to 8 weeks) for healing and symptomatic relief of erosive esophagitis (approved 2 Feb 00).

Irritable Bowel Syndrome

- Alosetron (Lotronex; Glaxo Wellcome): treatment of irritable bowel syndrome (IBS) in women whose predominant symptom is diarrhea (approved 9 Feb 00) - this drug was withdrawn by the manufacturer 30 Nov 00

Ulcerative Colitis

- Balsalazide disodium (Colazal; Saliz Pharmaceuticals); treatment of mildly to moderately active ulcerative colitis [sulfa-free prodrug of 5-ASA] (approved 24 Jul 00)

Hematology/Oncology

Acute Myeloid Leukemia

- Gemtuzumab Ozogamicin (Mylotarg; Wyeth-Ayerst Labs); treatment of patients with CD33+ acute myeloid leukemia in first relapse who are >60 years of age and who are not candidates for cytotoxic chemotherapy (approved 17 May 00)

Acute Promyelocytic Leukemia

- Arsenic trioxide injectable (Trisenox; Cell Therapeutics); induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) (approved 25 Sep 00)

Cutaneous T-cell Lymphoma

- Bexarotene gel (Targretin gel; Ligand); topical treatment of cutaneous lesions in patients with early-stage (TNM Stage IA and IB) cutaneous T-cell lymphoma (CTCL) (approved 29 Jun 00)

Deep Vein Thrombosis

- Tinzaparin injection (Innohep; Dupont); treatment of acute symptomatic deep vein thrombosis (DVT) with or without pulmonary embolism when administered in conjunction with warfarin sodium (approved 18 Jul 00) - a new low molecular weight heparin (LMWH)

Hemophilia A

- Recombinant Antihemophilic Factor (ReFacto; Genetics Institute); control and prevention of hemorrhagic episodes and for short-term routine and surgical prophylaxis in patients with hemophilia A (approved 6 Mar 00)

Heparin-Induced Thrombocytopenia

- Argatroban injection (Acova; Texas Biotech/Smith Kline Beecham); prophylaxis or treatment of heparin-induced thrombocytopenia (HIT) (approved 30 Jun 00)

Prostate Cancer

- Leuprolide acetate implant (Viadur; Alza Corp); palliative treatment of advanced prostate cancer (approved 3 Mar 00); not yet commercially available
- Triptorelin pamoate injection (Trelstar depot; Pharmacia and Upjohn); palliative treatment of advanced prostate cancer (approved 15 Jun 00)

Infectious Disease

- Linezolid (Zyvox; Pharmacia and Upjohn); treatment of adults with community acquired pneumonia, nosocomial pneumonia, and uncomplicated skin/skin structure infections, MRSA infections, and VRE infections (approved 18 Apr 00)
- Atovaquone / proguanil (Malarone; Glaxo Wellcome); prevention and treatment of acute, uncomplicated Plasmodium falciparum malaria (approved 14 July 00)
- Pneumococcal 7-valent Conjugate Vaccine [diphtheria CRM 197 Protein] (Prevnar; Lederle); Immunization of infants 2,4,6 and 12-15 months of age to prevent invasive pneumococcal disease (approved 17 Feb 00)

HIV Infection

- Lopinavir and ritonavir solution (Kaletra; Abbott); treatment of HIV-1 infection in adults and pediatric patients age six months and older (approved 15 Sep 00)
- Abacavir/lamivudine/zidovudine tablets (Trizivir; Glaxo Wellcome); alone or in combination with other anti-retrovirals for treatment of HIV-1 infection (approved 14 Nov 00) - triple combination of nucleoside reverse transcriptase inhibitors

New Drugs and Biologics of 2000

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Infertility

- Cetrorelix injectable (Cetrotide; Asta Medica); prevention of premature LH surges in women undergoing controlled ovarian stimulation (approved 11 Aug 00)
- Gonadotropin, chorionic human recombinant injectable (Ovidrel; Serono Labs); induction of final follicular maturation and early luteinization in infertile women as part of an assisted reproductive technology program (approved 20 Sep 00)

Mental Health

- Fluoxetine (Sarafem; Eli Lilly); treatment of premenstrual dysphoric disorder (PMDD) (approved 6 Jul 00) - chemically identical to Prozac™; specialized packaging with separate labeling for PMDD

Neurology

Alzheimer's Disease

- Rivastigmine (Exelon; Novartis); mild to moderate Alzheimer's dementia (approved 21 Apr 00)

Attention Deficit Disorder

- Methylphenidate HCl extended release tablet (Concerta; Alza); treatment of attention deficit disorder (approved 1 Aug 00)

Migraine Prophylaxis

- Divalproex sodium ER tablets (Depakote ER; Abbott), for prophylaxis of migraines in adults (approved 13 Oct 00)

Seizure Disorder

- Oxcarbazepine (Trileptal; Novartis); for monotherapy/adjunctive therapy in adults with partial seizures; or adjunctive therapy in the treatment of partial seizures in children ages 4-16 with epilepsy (approved 14 Jan 00)
- Zonisamide (Zonegran; Elan Corp); adjunctive therapy in adults with partial seizures (approved 27 Mar 00)

Nephrology

- Doxercalciferol injectable (Hectoral; Bone Care International); reduction of elevated iPTH levels in the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis (approved 6 Apr 00)
- Sevelamer (Renagel; Geltex Pharmaceuticals); reduction of serum phosphorus in patients with end-stage renal disease (Approved 12 Jul 00)
- Iron sucrose injectable (Venofer; Luitpold Pharmaceuticals); treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving erythropoietin; does not require a test dose prior to administration (approved 6 Nov 00)

Ophthalmology

- Levobetaxolol (Betaxon; Alcon Labs): lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension (approved 23 Feb 00)
- Verteporfin injectable (Visudyne; QLT PhotoTherapeutics); age-related macular degeneration in patients with predominantly subfoveal choroidal neovascularization (approved 12 Apr 00)
- Unoprostone isopropyl (Rescula; Ciba Vision/Novartis); for lowering of intraocular pressure in patients with open-angle glaucoma (approved 3 Aug 00)
- Azelastine hydrochloride ophthalmic solution, 0.05% (Optivar; ASTA Medica); itching of the eye associated with allergic conjunctivitis (approved 22 May 00)
- Levofloxacin ophthalmic solution, 0.5%, (Quixin; Santen); bacterial conjunctivitis (approved 21 Aug 00)

Pulmonary

Allergic Rhinitis

- Triamcinolone nasal spray (Trinasal; Muro Pharmaceuticals): treatment of seasonal and perennial allergic rhinitis in adults and children >12 years of age (approved 4 Feb 00)

Asthma

- Beclomethasone dipropionate HFA inhalation aerosol, (QVar; 3M Pharma); maintenance treatment of asthma as prophylactic therapy, or for asthma patients who require systemic corticosteroid administration; (approved 15 Sep 00)
- Budesonide inhalation suspension (Pulmicort Respules; AstraZeneca); maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age); (approved 8 Aug 00)

Rheumatology

- Meloxicam (Mobic; Boehringer Ingelheim/Abbott Labs); relief of signs and symptoms of osteoarthritis (approved 13 Apr 00)
- Cevimeline (Evoxac; Snowbrand Pharmaceuticals); treatment of symptoms of dry mouth in patients with Sjögren's Syndrome (approved 11 Jan 00)

Urology

- BCG Live (PACIS; BioChem Pharma); treatment of carcinoma-in-situ (CIS) in the absence of associated invasive cancer of the bladder (approved 9 March 00)

Women's Health

- Estradiol / norethindrone acetate tablets (Activella; Pharmacia & Upjohn); for women with an intact uterus for the prevention of postmenopausal osteoporosis (approved 11 Apr 00)

New Drugs and Biologics of 2000

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- Estradiol cypionate, medroxyprogesterone acetate injection (Lunelle; Pharmacia and Upjohn) prevention of pregnancy (Pharmacia and Upjohn) (approved 5 Oct 00)
- Desogesterel/ethinyl estradiol tablets (Cyclessa; Organon); pregnancy prevention; first low dose (<30 mcg estrogen) triphasic oral contraceptive (approved 20 Dec 00); not yet commercially available
- Estradiol vaginal ring (Estring; Pharmacia and Upjohn); treatment of urogenital symptoms associated with post-menopausal vaginal atrophy (approved 5 Jan 00)

Other

- Eflornithine HCl 13.9% cream (Vaniqa; Bristol-Myers Squibb); reduction of unwanted facial hair in women (approved 28 Jul 00)
- Mifepristone (Mifeprex, RU-486; Danco Labs); medical termination of intrauterine pregnancy, through day 49 of pregnancy (approved 28 Sep 00)
- Crotalidae polyvalent immune Fab (ovine) (Crofab; Protherics Inc); treatment of minimal to moderate North American Crotalidae envenomation (approved 2 Oct 00)
- Polytetrafluoroethylene/perfluoroalkylpolyether cream (Skin exposure reduction paste against chemical warfare agents [SERPACWA]; USA Office Surgeon General; Provides for the use of SERPACWA only in conjunction with Mission Oriented Protective Posture (MOPP) gear to reduce or delay the absorption of chemical warfare agents through the skin when applied prior to exposure (17 Feb 00)
- Botulinum toxin type B injectable (Myobloc; Elan Corporation); symptomatic treatment of patients with cervical dystonia (spasmodic torticollis) (approved 12 Dec 00)

Focus on 8 new drugs reviewed at the Nov 2000 DoD Pharmacy & Therapeutics Committee Meeting

At the 16 Nov 00 DoD Pharmacy & Therapeutics (P&T) Committee meeting, a record number of new drugs—eighteen—were considered for formulary status on the National Mail Order Pharmacy (NMOP) Formulary and the DoD Basic Core Formulary (BCF). In this article, we concentrate on eight drugs that are expected to have the most impact on the Military Health System or which raised issues concerning BCF status. DoD P&T committee actions at the November 2000 meeting are listed in **bold**print at the end of each section. Please see Appendix A of the Nov 00 DoD P&T Committee meeting minutes (**www.pec.ha.osd.mil/PT_Committee.htm**) for more details.

Metformin / glyburide combination (Glucovance; Bristol-Myers Squibb)

Metformin / glyburide (Glucovance; Bristol-Myers Squibb) was approved 31 July 00 for initial therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes; and second-line therapy when diet, exercise and initial treatment with a sulfonylurea or metformin do not result in adequate glycemic control in patients with type 2 diabetes. Glucovance® tablets are available in 1.25/250 mg, 2.5/500 mg, and 5/500 mg glyburide / metformin.

Two trials were conducted to gain FDA approval for Glucovance®, one as initial therapy (N=806) and one as second-line therapy (N=639). In both trials, Glucovance® resulted in significant decreases in HbA1c compared to placebo or to monotherapy with metformin or glyburide. In the initial therapy trial, Glucovance® was significantly more efficacious in lowering HbA1c levels than monotherapy with glyburide or metformin only in patients with baseline HbA1c levels over 9%, a level at which one would not expect monotherapy to be fully effective.

Approximately 1.25 million diabetics in the U.S. take a combination of metformin and a sulfonylurea as separate products. Use of the combination product would simplify drug regimens, but clinical trials have not yet shown that the single combination product will significantly improve patient adherence compared to the individual components given separately. It also remains to be seen whether improved adherence will result in clinically significant reductions in HbA1c, since the lack of dosing flexibility with the combination product may affect the ability to attain optimum glycemic control. A third unanswered question is whether initial use of the combination product will give the same duration of glycemic control as the usual approach of starting with a single agent. This can only be addressed by long-term studies.

The DoD prime vendor price for Glucovance® is $29.00 per bottle of 100 for all strengths ($0.29 each). For comparison, a 500-mg tablet of metformin costs approximately $0.30; glyburide ranges from $0.01 - $0.03 per tablet, depending on strength.

Metformin (Glucophage®, Bristol-Myers Squibb) lost exclusivity in Sep 00, after expiration of a 6-month pediatric

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exclusivity extension. Generic competition is expected in the summer of 2001. Glucovance® and extended release metformin (see entry below) are dosage forms that may enable the manufacturer to maintain market share in the face of generic competition. While the combination product may have some advantages related to convenience and patient adherence to therapy in patients taking both products, the benefit gained may be very small compared to the potential cost difference between Glucovance and glyburide / metformin as individual components once a metformin generic is available. **At the Nov 00 DoD P&T Committee meeting, the committee decided not to add Glucovance® to the BCF. Both glyburide and metformin have individual listings on the BCF. Glucovance® was added to the NMOP Formulary.**

Metformin extended release tablets (Glucophage XR; Bristol-Myers Squibb)

Metformin extended release 500-mg tablets (Glucophage XR; Bristol-Myers Squibb) were approved 13 Oct 00 to improve glycemic control in patients with type 2 diabetes; the indications for use are identical to the indications for immediate release metformin. The once-daily extended release tablets slowly release the drug by diffusion in a pH-independent manner.

Patients enrolled in the clinical trials used to gain FDA approval (see product labeling) were relatively well-controlled diabetics with a baseline HbA1c between 7 and 8.3% and a baseline fasting plasma glucose of 176 to 190 mg/dL. The trials showed reductions in HbA1c and fasting plasma glucose in patients taking Glucophage XR® compared to placebo. Product labeling also contains results of a 24-week trial of Glucophage XR 1000- or 1500-mg once daily vs. immediate release metformin (500 mg twice daily) in patients who had received immediate release metformin 500 mg twice daily for at least 8 weeks. Patients in all three groups experienced small increases in HbA1c (the baseline was about 7%) and fasting plasma glucoses after 24 weeks; the increase in HbA1c was statistically significant only in the 1000-mg once daily group.

Although it appears from package labeling that the incidence of GI adverse effects may be lower with the metformin extended release (ER) than with the immediate release preparation, direct comparison of the two formulations is not possible because no head-to-head data are presented. Like immediate release metformin, the extended release tablets require titration to the effective dose in order to minimize gastrointestinal adverse effects.

Metformin ER tablets are large, which could pose problems for patients with swallowing difficulties, particularly as patients must take up to four 500-mg tablet at one time with the evening meal. The DoD prime vendor price for Glucophage XR® is $0.29 per 500-mg tablet, slightly less than immediate release metformin (Glucophage®), at $0.30 per 500-mg tablet.

At the Nov 00 DoD P&T Committee meeting, the committee agreed that while the extended release preparation is slightly less costly than immediate release metformin (Glucophage®) 500-mg tablets at the moment, it did not appear to offer enough additional benefit to offset the potential for higher costs once a generic metformin product becomes available. **The committee excluded Glucophage XR® from the BCF listing for metformin. MTFs are not required to have this extended release product on their formularies, but may add it if they so desire. Glucophage XR® was added to the NMOP Formulary.**

Alendronate for once-weekly treatment / prevention of osteoporosis

Alendronate 35- and 70-mg (once-weekly) tablets (Fosamax; Merck) were approved 20 Oct 00 for prevention (35-mg) or treatment (70 mg) of osteoporosis in postmenopausal women. Alendronate is also available in 5-, 10-, and 40-mg tablets. The 40-mg tablets, which are indicated for Paget's disease, are now available only from one specialty pharmacy (CVS Procare) or through the NMOP for DoD beneficiaries (see Nov 00 DoD P&T Committee minutes for more details).

The 70-mg weekly dose of alendronate has been shown to be equivalent to 10 mg daily for treatment of osteoporosis, and the 35-mg weekly dose has been shown to be equivalent to 5 mg daily for prevention of osteoporosis. In each case, one-year, double-blind trials reported similar increases in lumbar spine bone mineral density with the once-weekly and once-daily regimens.

The rationale for once-weekly as opposed to once-daily administration of alendronate pertains to the fact that the half-life of alendronate on bone surfaces is several weeks, which implies that once-weekly administration of alendronate should inhibit bone resorption to a similar degree and result in similar effects on bone mass and strength compared to more frequent dosing. Weekly administration may also decrease the potential for esophageal irritation by minimizing repeated insult and/or by allowing time for healing between doses. Once-weekly administration of alendronate appears likely to offer compliance / convenience advantages and to possibly reduce the risk of adverse reactions, although the dosing instructions for the once-weekly formulation are identical to the once-daily preparation (i.e., take with a full glass of water while standing and avoid lying supine for 30 minutes following administration).

A 30 Oct 00 professional response letter from Merck cites results from market surveys of physicians and patients. Of physicians surveyed, 89% expected that women's willingness to initiate alendronate therapy would increase with a once-weekly dosage form. Of patients surveyed, 72% indicated they would "definitely" or "most likely" switch to a once-weekly regimen (n=70).

The DoD prime vendor price/FSS price for alendronate 70

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mg is the same as the price for seven of the 10-mg tablets. (A blister pack of four 70-mg tabs: $31.33; 28 10-mg tablets $31.34.) The 70-mg tablets (for treatment of osteoporosis) should be on pharmacy shelves soon if not already available; the 35-mg tablets (for prevention) are expected in early 2001.

At the Nov 00 DoD P&T Committee meeting, the committee decided that the existing BCF listing for alendronate will include the once-weekly formulations. This was based on the fact that once weekly administration appears to be as effective as once daily and may have tolerability/safety advantages, while the cost per week for the once-weekly and once-daily tablets is the same. The earliest patent expiration listed in the FDA Orange Book for Fosamax® is 2007. The once-weekly formulations of Fosamax® are available through the NMOP.

An extended release preparation of divalproex sodium for migraine prophylaxis

Divalproex sodium 500-mg extended release tablets (Depakote ER; Abbott) were approved 13 Oct 00 for prophylaxis of migraines in adults. Unlike the delayed-release product (Depakote®), which has FDA approval for prophylaxis of migraine headaches in adults, treatment of manic episodes associated with bipolar disorder, and seizure disorder, Depakote ER® is FDA-approved only for the migraine prophylaxis indication only. Depakote ER® tablets are not bioequivalent to Depakote® delayed-release tablets.

Depakote ER® was approved for migraine prophylaxis based on one multicenter, randomized, double-blind, placebo-controlled, parallel-group trial demonstrating a significant decrease in headache rate with Depakote ER® compared to placebo.

At the Nov 00 DoD P&T Committee meeting, the committee decided that the existing BCF listing for divalproex sodium will include Depakote ER®, since the extended release tablets may have some convenience advantages (two 500-mg tablets once daily as opposed to one 500-mg Depakote® tablet twice daily) for migraine prophylaxis and are cost-neutral. Pricing for two of the 500-mg extended release tablets is approximately the same as two of the 500-mg delayed-release tablets ($0.70 per tablet or approximately $1.40 per day). The earliest patent expiration listed in the FDA Orange Book for Depakote® is 2008. **Depakote ER® was added to the NMOP Formulary.**

A new extended release formulation of methylphenidate for ADHD

Methylphenidate HCl extended release tablets (Concerta; Alza; Schedule II) were approved 1 Aug 00 for the treatment of attention deficit hyperactivity disorder (ADHD). Concerta® is not bioequivalent to other sustained release methylphenidate products. The formulation consists of an immediate release component and an extended release component, which provides for an initial morning effect followed by extended release of medication over an approximately 12-hour period.

Concerta® has been shown to be as efficacious in the treatment of children with ADHD as immediate release methylphenidate given three times daily, but has not been tested against other controlled release methylphenidate formulations. Immediate release formulations of methylphenidate have a short duration of action and require multiple daily dosing. Sustained and extended release dosage forms were formulated to lengthen the duration of action and decrease the frequency of administration. However, the slower onset and flat release profile of sustained release formulations, intended to minimize the fluctuation between peak and trough concentrations, may not result in sufficient increase in brain catecholamines to produce the same clinical effects as immediate release formulations, especially during the afternoon. The adverse effects associated with immediate release and sustained release methylphenidate formulations appear to be similar, although the severity of some adverse effects may be less with the sustained release formulations.

At the Nov 00 DoD P&T Committee meeting, the committee decided that the existing BCF listing for methylphenidate will include Concerta®, since once-daily dosing of Concerta has the potential to simplify dosing and obviate the need for children to take doses during the school day. The committee pointed out that this is a quality of life issue that has a direct impact on active duty dependents and active duty personnel. Recent analysis of MTF prescription data from the Uniformed Services Prescription Database confirms that noontime methylphenidate doses are frequently prescribed, even when sustained release dosage forms are used.

Concerta® is approximately 57% more costly than typical regimens of sustained release plus immediate release methylphenidate. The DoD prime vendor price for the once daily 18- and 36-mg tablets of Concerta® is $1.30-$1.38, compared to approximately $0.88 for a fairly typical regimen of methylphenidate sustained release 20 mg in the AM and 10 mg immediate release twice daily. Clinical studies and input from providers assessing the extent to which Concerta® is successful in eliminating school doses are not yet available. Concerta® is available through the NMOP.

A new low-molecular weight heparin (LMWH) for treatment of DVT

Tinzaparin injection (Innohep; Dupont) was approved 18 Jul 00 for treatment of acute symptomatic deep vein thrombosis (DVT) with or without pulmonary embolism, when administered in conjunction with warfarin sodium. Safety and effectiveness of tinzaparin for the treatment of DVT were established in hospitalized patients. Tinzaparin is not indicated for prophylaxis following orthopedic or

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abdominal surgeries or for use in unstable angina. A Dupont representative said that the company does not currently plan on pursuing these indications. European data supports the efficacy of tinzaparin for prophylaxis of DVT following orthopedic and abdominal surgery. Tinzaparin is dosed once daily for the treatment of DVT.

The drug has been available in Europe and Canada for several years. Acquisition of marketing rights by Dupont, manufacturer of the innovator warfarin product Coumadin®, enables the company to market the products on the basis of "continuity of care" between parenteral and oral anticoagulation therapy.

Tinzaparin is only available in multi-dose vials, unlike the other available low-molecular weight heparins, enoxaparin (Lovenox) and dalteparin (Fragmin), which are available in unit-dose syringes. (Dalteparin is also available in multi-dose vials). Patients must be instructed on the proper technique to draw up individual doses of tinzaparin in a syringe. Tolerability may be a minor differentiating factor among the agents. The unit-dose syringes of enoxaparin and dalteparin have very small needles and may be less painful on injection. Use of multi-dose vials of tinzaparin and dalteparin requires a TB syringe for administration.

At the Nov 00 DoD P&T committee meeting, the committee modified the existing BCF requirement that MTFs have "at least one of the following products on the MTF formulary: ardeparin (Normiflo®); dalteparin (Fragmin®); danaparoid (Orgaran®); or enoxaparin (Lovenox®). MTFs will select the specific brand." The requirement was amended to include tinzaparin as an option and to remove ardeparin, which is no longer available. The committee also agreed that the class should be reviewed to assess the need for having the LMWHs available through the NMOP, the need for a prior authorization process at the NMOP/retail network to control inappropriately extended use, and the potential for contracting/incentive price agreements to reduce the unit cost of LMWH therapy. The committee agreed that such an action could be done in conjunction with the VA, which is currently completing a LMWH clinical review.

Like the other LMWHs, tinzaparin is not available through the NMOP at this time.

A new bile acid sequestrant for hyperlipidemia

Colesevelam hydrochloride (Welchol; GelTex Pharma/Sankyo Parke Davis), a bile-acid sequestrant, was approved 30 May 00 as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia, administered alone or in combination with an HMG-CoA reductase inhibitor. Colesevelam is not absorbed from the GI tract and is excreted exclusively in the feces. Colesevelam is dosed as 3 tablets twice daily with meals or 6 tablets once daily with a meal (may increase to 7 tablets daily).

Colesevelam produces modest lowering of LDL-cholesterol and total cholesterol and slight increases in HDL-cholesterol. Like other bile acid sequestrants, it may increase triglyceride levels. Combination therapy with colesevelam and HMG-CoA reductase inhibitors (atorvastatin, lovastatin, or simvastatin) has been assessed in three studies. In general, colesevelam doses of 2.3 to 3.8 g per day resulted in additional 8% to 16% reductions in LDL-cholesterol compared to the HMG-CoA reductase inhibitor alone. The effects of colesevelam have not been directly compared to those of cholestyramine and colestipol. All three agents appear to produce similar effects on total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels.

Colesevelam tablets may be a more convenient dosage form than the powder/granules for oral suspension formulations of cholestyramine (Questran, others) or colestipol (Colestid). (Colestipol is also available in tablet form, but has been reported to cause difficulty swallowing and esophageal obstruction due to the large size of the tablets.) Colesevelam may also have an advantage over cholestyramine and colestipol regarding constipation, the most common side effect of cholestyramine and colestipol and one that may require dosage reduction or discontinuation of therapy.

In addition, colesevelam may prove to have advantages over the other bile acid sequestrants with regard to drug interactions, although caution is advised until more post-marketing experience accumulates. The other bile acid sequestrants, cholestyramine and colestipol, should be administered at least 4 to 6 hours before or 1 hour after other medications to reduce their impact on the absorption of other medications. Such a recommendation has not been made for colesevelam, but the precaution is logical until proven unnecessary. Colesevelam does not appear to affect the bioavailability of digoxin, lovastatin, metoprolol, quinidine, valproic acid, or warfarin.

At the Nov 00 DoD P&T Committee meeting, the committee decided not to add colesevelam to the BCF. Colestipol is currently on the BCF. The committee asked the PEC to obtain more information to establish if a bile acid sequestrant continues to be required on the BCF and if colesevelam's apparent advantages of improved tolerability, reduced constipation, and fewer drug interactions make it a better choice. The committee agreed that the PEC should wait until the Adult Treatment Panel III Guidelines are out and bring the issue back to the committee for consideration. **Colesevelam was added to the NMOP Formulary.**

A non-CFC beclomethasone MDI

Beclomethasone dipropionate HFA inhalation aerosol (QVar; 3M Pharma) was approved 15 Sep 00 for the maintenance treatment of asthma as prophylactic therapy. QVar® is also indicated for asthma patients who require

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systemic corticosteroid administration, where adding QVar® may reduce or eliminate the need for the systemic corticosteroids. This product does not contain chlorofluorocarbons (CFCs), which have aroused environmental concerns. More information on the FDA's plan to deal with the issue of CFCs in metered dose inhaler (MDI) products is available on the FDA website at **www.fda.gov/cder/mdi/default.htm**.

QVar® is not AB rated to the other two beclomethasone MDIs (Vanceril® and Beclovent®). The QVar® vehicle is a solution, rather than a suspension. QVar® may be more potent than the other beclomethasone MDIs. QVar is available as a 40 mcg/inhalation, 100-actuation inhaler device at a cost of $15.97 or as an 80 mcg/inhalation, 100-actuation device at a cost of $22.23.

At the Nov 00 DoD P&T Committee meeting, the committee decided not to add QVar® to the BCF. They added the drug to the NMOP Formulary and established quantity limits for the NMOP and the retail network. See **www.pec.ha.osd.mil/qtylimit.htm** for more information on quantity limits.

In the News

VA/DoD Clinical Practice Guideline for Diabetes

VA/DoD Clinical Guideline Implementation to start with Satellite Broadcast

A satellite broadcast on 31 Jan 2001, 1300 - 1500 EST, will kick-off system-wide implementation of the VA/DoD Diabetes Clinical Practice Guideline (CPG) in Army Medical Department (AMEDD) facilities. The satellite broadcast, developed by the VA and the AMEDD, includes presentations by DoD and VA guideline champions and interviews with personnel with experience in implementing the guideline. Taped re-broadcasts are planned for 8 Feb 2001 and 20 February 2001--please see the MEDCOM Quality Management Office website at **www.cs.amedd.army.mil/Qmo** (click on "Practice Guidelines") for more details.

The *VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus in the Primary Care Setting* is available on the MEDCOM Quality Management Office website in both a web-navigable version and in MS Word format. Also available on the site: performance metrics, provider documentation forms and reminder materials, patient education materials, implementation tools, and MTF innovations for diabetes care.

PDTS Corner

Update on the Pharmacy Data Transaction Service

Sonya Edom, Customer Service Supervisor at the PDTS Customer Service Support Center (CSSC), reports that 18 CHCS Host sites are now active on PDTS, in addition to the National Mail Order Pharmacy and two Managed Care Support Contractors. PDTS is now processing from 52,000 to 60,000 transactions every weekday. The average transaction time is 3.18 seconds (from the time the user files the prescription until they receive a response from PDTS). A total of 302 potential level 1 drug-drug interactions have been detected to date.

Four to five CHCS host sites will be activating PDTS each week--watch for e-mail updates from your Specialty Leader for PDTS activations near you!

The PDTS CSSC reports no major issues or concerns with any PDTS activation to date, but Ms. Edom wants to remind everyone to

"Keep your CHCS database clean!"

Lessons Learned from MTF Activations of PDTS to Date

This file of actual problems encountered during activation of PDTS and how they have been resolved is a "living document" which will be updated as often as needed. The file may be downloaded in MS Word format from: **www.pec.ha.osd.mil/Updates/0102web/PDTS_Lessons_Learned.doc**.

For more information about PDTS:

Visit the Pharmacy Data Transaction Service Page on the TRICARE Pharmacy Site at **www.tricare.osd.mil/pharmacy/data_trans.htm**

Or see back issues of the PEC Update at **www.pec.ha.osd.mil/ac03000.htm**:

- **December 2000:** Accessing the TMSSC InfoNet site
- **October 2000:** More info on PDTS, change of access numbers and hours of operation for the CSSC, provider validation Ad Hoc report
- **January 2000:** The PDTS Customer Service Support Center